Synthesis of Enantiomerically Pure Δ²-Isoxazolines† *via* Sulphinyl Derivatives

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Optically active 3-sulphinylmethyl-Δ²-isoxazolines† allow an easy entry to enantiomerically pure Δ²-isoxazolines and to the corresponding β-hydroxy ketones.

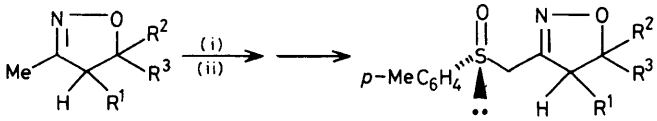
The control of relative and absolute stereochemistry in the construction of a sequence of asymmetrically substituted carbon atoms in acyclic molecules is still a challenging topic in synthesis.[1]

In this context Δ²-isoxazolines† have recently received a great deal of interest. These compounds, which can be obtained by regioselective and stereocontrolled cycloadditions of nitrile oxides to olefins,[2] were shown to represent an easy entry to diastereoisomerically homogeneous β-ketols[3] and γ-amino alcohols.[4] Therefore, the development of a successful strategy for the synthesis of optically active Δ²-isoxazolines was of interest to us.‡

We report here that diastereoisomerically and/or enantiomerically pure Δ²-isoxazolines can be easily prepared *via* a new class of sulphinyl derivatives *i.e.* 3-(tolylsulphinylmethyl)-Δ²-isoxazolines.

Indeed, *exo*-metallation[6] of racemic 3-methyl-Δ²-isoxazolines[7] (**1**)—(**6**) and subsequent reaction with (−)-(*S*)-menthyl toluene-*p*-sulphinate affords in excellent yields compounds (**7a,b**)—(**12a,b**) as mixtures of diastereoisomers (Scheme 1).

The extent of chiral discrimination in this reaction, not unexpectedly, is low, ranging from 8 to 20%. However, the individual stereoisomers can be separated by gravity or flash chromatography and the diastereoisomeric purity at all their stereocentres easily checked by ^{1}H n.m.r. spectroscopy. Yields, diastereoisomeric ratios, melting points, and optical rotations of compounds (**7**)—(**12**) are reported in Table 1.



(**1**); (**7a,b**) R¹ = R² = H; R³ = Bu^t
(**2**); (**8a,b**) R¹ = R² = H; R³ = n-C_5H_{11}
(**3**); (**9a,b**) R¹ = R² = −[CH_2]$_3$−; R³ = H
(**4**); (**10a,b**) R¹ = Me; R² = *p*-MeOC_6H_4; R³ = H
(**5**); (**11a,b**) R¹ = *p*-MeOC_6H_4; R² = Me; R³ = H
(**6**); (**12a,b**) R¹ = H; R² = Me; R³ = Ph

Scheme 1. *Reagents*: (i), lithium di-isopropylamide (LDA); (ii), menthyl toluene-*p*-sulphinate.

The relative stereochemistry at C-4 and C-5 of the isoxazoline ring is pre-determined by the configuration of the olefin which undergoes the cycloaddition. The absolute configuration of the sulphoxide in (**7**)—(**12**) can be inferred as (*R*) from that of the starting sulphinate ester, as commonly accepted for a number of related Andersen-type syntheses which are known to proceed with complete inversion of chirality at sulphur.[8] Therefore our reaction generates only two dia-

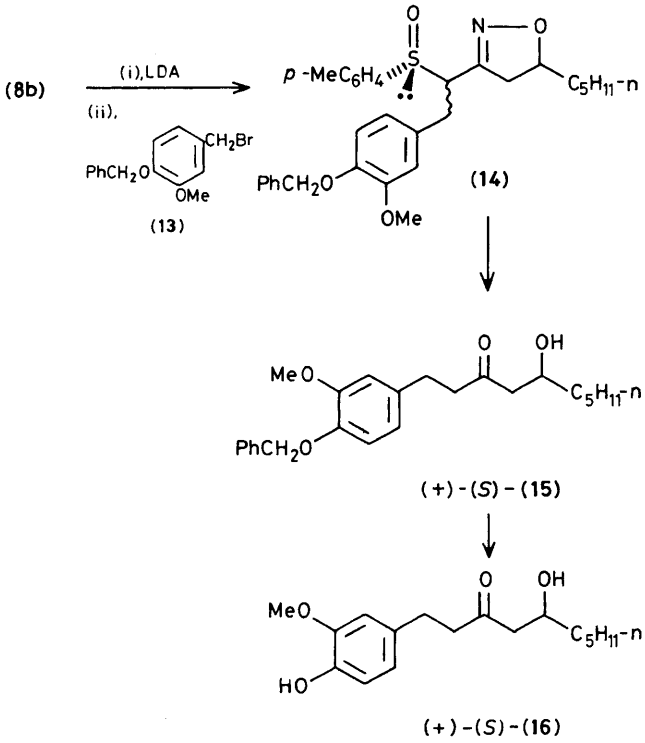
† Now 4,5-dihydroisoxazolines, see *Pure Appl. Chem.*, 1983, **55**, 409.

‡ During the completion of this work an application of chiral isoxazolines to the asymmetric synthesis of β-hydroxy acids was published.[5]

Table 1. Synthesis of 3-(tolylsulphinylmethyl)-Δ^2-isoxazolines (**7a,b**)—(**12a,b**).[a]

Compound	Yields (%)	Diastereoisomeric[b] ratios **a** : **b**	Diastereoisomer **a**[c]		Diastereoisomer **b**[c]	
			$[\alpha]_D^{23}$ [d]	M.p./°C	$[\alpha]_D^{23}$ [d]	M.p./°C
(**7a,b**)	67	46 : 54	+337.5	94—96	+140.3	79—81
(**8a,b**)	80	45 : 55	+297.5	70—72	+134.4	63—65
(**9a,b**)[e]	84	40 : 60	+279.0	78—81	+ 79.8	82—84
(**10a,b**)[f]	75	55 : 45	+328.3	130—131	— [g]	—
(**11a,b**)[f]	76	46 : 54	+ 83.2	118—120	+262.2	89—91
(**12a,b**)	95	42 : 58	+263.8	102—104	+167.5	100—102

[a] Reaction carried at −90 °C under argon in tetrahydrofuran with 2 mol. equiv. of metallated (**1**)—(**6**) and 1 mol. equiv. of sulphinate ester. All new compounds gave analytical and spectral data in agreement with the proposed structures. [b] As determined by ^{1}H n.m.r. spectroscopy. [c] Diastereoisomer **a** is the one eluted first and diastereoisomer **b** is the one eluted second in column chromatography. [d] *c* 1 in $CHCl_3$. [e] *cis* relative stereochemistry at C-4 and C-5 of the isoxazoline ring. [f] *trans* relative stereochemistry at C-4 and C-5 of the isoxazoline ring. [g] Compound (**10b**) could not be isolated free of (**10a**).



stereoisomers, the separation of which yields enantiomerically pure compounds. Conversion of compounds (**7**)—(**12**) into optically pure Δ^2-isoxazolines is cleanly performed in nearly quantitative yields by reductive desulphurization with Na–Hg in dry methanol in the presence of NaH_2PO_4.§

Using this method, (**10a**), the dextrorotatory enantiomer of (**4**),¶ $[\alpha]_D^{23}$ + 208.2° (*c* 1 in $CHCl_3$), was obtained in 90% yield. Analogously, both enantiomers of (**5**) were synthesized from (**11a**) and (**11b**): they had $[\alpha]_D^{23}$ −269.5° (*c* 0.2 in $CHCl_3$) and +270.6° (*c* 0.25 in $CHCl_3$), respectively. It should be noted that neither epimerization on the C-4 position of the isoxazoline nor reductive opening of the N–O bond[10] was observed under these conditions.

Finally we note that both desulphurization and unmasking of the ketol moiety embedded in the heterocyclic ring could be simultaneously performed by Raney nickel-catalysed reactions of (**7**)—(**12**). This allowed the direct conversion (80% yield) of compound (**12b**) into 4-hydroxy-4-phenylpentan-2-one,[11] $[\alpha]_D^{23}$ −5.1°; $[\alpha]_{365}^{23}$ + 37.8° (*c* 1 in $CHCl_3$). This same compound was obtained *via* Na–Hg desulphurization (98% yield) of isoxazoline (−)-(**6**), $[\alpha]_D^{23}$ −40.0° (*c* 1 in $CHCl_3$) and subsequent Raney nickel-catalysed ring opening.[3]

(+)-(*S*)-Gingerol (**16**)[12] was synthesised in three steps starting from (**8b**) using this method. Alkylation of (**8b**) with the bromide (**13**) in the presence of hexamethylphosphoramide yielded sulphoxide (**14**) in 80% yield as a 6 : 4 mixture of epimers at the carbon α to the sulphinyl group. This mixture was converted (94% yield) by Raney nickel-catalysed hydrogenation in acidic medium[3] into (+)-(*S*)-(**15**), m.p. 70 °C, $[\alpha]_D^{23}$ +19.6° (*c* 0.4 in $CHCl_3$), enantiomeric excess (e.e.) >96%.[12] This compound can then be de-benzylated to give (+)-(*S*)-(**16**), $[\alpha]_D^{23}$ +25.7° (*c* 1 in $CHCl_3$), with unchanged e.e.** as described elsewhere.[12]

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§ 1.5 g of 8% Na–Hg, 1.2 g of dry NaH_2PO_4, and 15 ml of methanol per 1.0 mmol of substrate at 0 °C; reaction time 30 min.

¶ Enantiomerically pure (**4**) can be a useful intermediate for the synthesis of nikkomycin B.[9]

** Maximum reported rotation $[\alpha]_D^{24}$ +25.1° (*c* 1 in $CHCl_3$).[12]